**AWARD NUMBER:** W81XWH-16-C-0161

**TITLE:** Hypothermia for Patients Requiring Evacuation of Subdural Hematoma: Effect on Spreading Depolarizations

**PRINCIPAL INVESTIGATOR**: Jed A. Hartings, PhD

**RECIPIENT:** University of Cin**cinnati**
**Cincinnati, OH 45220**

**REPORT DATE:** October 2017

**TYPE OF REPORT:** Annual

**PREPARED FOR:** U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

# REPORT DOCUMENTATION PAGE

*Form Approved*
*OMB No. 0704-0188*



| 1. REPORT DATE | 2. REPORT TYPE | 3. DATES COVERED |
|---|---|---|
| October 2017 | Annual | 30 Sep 2016 – 29 Sep 2017 |

**4. TITLE AND SUBTITLE**

Hypothermia for Patients Requiring Evacuation of Subdural Hematoma: Effect on Spreading Depolarizations

**5a. CONTRACT NUMBER**
W81XWH-16-C-0161

**5b. GRANT NUMBER**

**5c. PROGRAM ELEMENT NUMBER**

**6. AUTHOR(S)**
Jed A. Hartings, PhD

E-Mail: jed.hartings@uc.edu

**5d. PROJECT NUMBER**

**5e. TASK NUMBER**

**5f. WORK UNIT NUMBER**

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**

University of Cincinnati
2600 Clifton Ave
Cincinnati, OH 45220-2872

**8. PERFORMING ORGANIZATION REPORT NUMBER**

**9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)**

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

**10. SPONSOR/MONITOR'S ACRONYM(S)**

**11. SPONSOR/MONITOR'S REPORT NUMBER(S)**

**12. DISTRIBUTION / AVAILABILITY STATEMENT**

Approved for Public Release; Distribution Unlimited

**13. SUPPLEMENTARY NOTES**

**14. ABSTRACT**

This report describes Year 1 progress in a sub-study of the HOPES trial to assess the effects of hypothermia on the pathologic mechanism of spreading depolarizations (SD). HOPES is a randomized multi-center clinical study of very early hypothermia in patients with traumatic brain injury who require emergent surgical evacuation of a subdural hematoma. In this period, we developed methods and manuals for the use of electrocorticography to monitor SD, and incorporated procedures into HOPES protocols and databases. Subaward contracts were established and local ethical study approvals were obtained at three of four proposed study sites; a fourth site has withdrawn from the study and a replacement has been identified. The protocol, utilizing exception from informed consent (EFIC), was submitted to the Office of the Secretary of the Army for approval and remains under review. If approval is received, site initiation visits will be completed and sites will be opened for enrollment.

**15. SUBJECT TERMS**
traumatic brain injury; subdural hematoma; electroencephalography; spreading depression; spreading depolarization; therapeutic hypothermia; craniotomy

| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT | 18. NUMBER OF PAGES | 19a. NAME OF RESPONSIBLE PERSON |
|---|---|---|---|---|---|
| a. REPORT | b. ABSTRACT | c. THIS PAGE | | | USAMRMC |
| U | U | U | UU | 10 | 19b. TELEPHONE NUMBER *(include area code)* |

## TABLE OF CONTENTS


| | Page No. |
|---|---|
| 1. Introduction | 4 |
| 2. Keywords | 4 |
| 3. Accomplishments | 4 |
| 4. Impact | 7 |
| 5. Changes/Problems | 7 |
| 6. Products | 8 |
| 7. Participants & Other Collaborating Organizations | 8 |
| 8. Special Reporting Requirements | 9 |
| 9. Appendices | 9 |

## 1. INTRODUCTION:

HOPES (Hypothermia for Patients Requiring Evacuation of Subdural Hematoma) is a privately funded, prospective, multi-center randomized trial to determine the effects of very early cooling in the specific pathoanatomic subgroup of traumatic brain injury (TBI) patients undergoing surgical evacuation of acute subdural hematomas (ASDH). The study is conducted under Exception From Informed Consent (EFIC) due to the short time window for patient enrollment (5 hr post-TBI). Patients requiring evacuation of ASDH are randomized 1:1 to (a) normothermia at 37 C, or (b) hypothermia induced to 35 C before surgery and maintained at 33 C for at least 48 hr. Temperatures are managed in both groups by intravascular catheters and neurologic outcomes are assessed using the Glasgow Outcome Score-Extended at 6 months. The ***hypothesis of the present study*** is that a mechanism of therapeutic benefit of hypothermia is through suppression of spreading mass neuronal depolarizations, a mechanism of secondary damage in injured cerebral cortex. The ***objective*** is to determine whether very early cooling in the HOPES trial is associated with reduced incidence of spreading depolarizations compared to normothermia treatment. To achieve this objective, spreading depolarizations will be monitored by electrocorticography at four centers in the HOPES trial, as an optional observational monitoring component of the HOPES protocol. Electrocorticography electrode arrays will be placed on the brain after surgical ASDH evacuation, and spreading depolarizations will be monitored during the post-operative period of temperature management in the intensive care unit for a minimum of 48 hr. Recordings will then be scored for the occurrence and severity of spreading depolarizations by off-line, off-site review that is blinded to randomization and patient outcomes. The results will be compared with 6-month neurologic outcomes and between normothermia and hypothermia treatment arms.

## 2. KEYWORDS:

traumatic brain injury; subdural hematoma; electroencephalography; spreading depression; spreading depolarization; therapeutic hypothermia; normothermia; controlled normothermia; temperature management; mass lesion; craniotomy;

## 3. ACCOMPLISHMENTS:

### Major goals of the project

The major goals of the project are to determine:

1) Whether spreading depolarizations are less common in patients treated with hypothermia compared to normothermia (a) during temperature management and (b) after temperature management
2) Whether the burden of spreading depolarizations (during and after temperature management and in total) is associated with long-term neurologic outcome, and whether such association is dependent or independent of temperature management protocol

These goals will be accomplished by implementing electrocorticography (ECoG) monitoring at 4 study sites of the HOPES trial: University of Cincinnati (UC), University of Pittsburgh (UP), University of Texas at Houston (UT-H), and University of Miami (UM). UC is the coordinating center for the ECoG component of the study and will work closely with UT-H as the coordinating center for HOPES. The work is organized into major tasks to be accomplished in a 4-year

performance period. These are shown in the chart below with expected and actual times of task completion.

| TASK / MILESTONE | EXPECTED TIMELINE (months) | COMPLETION |
|---|---|---|
| 1. Develop Case Report Forms (CRFs) and implement web-based database in RedCap (Research Electronic Capture, Vanderbilt University) utilizing TBI Common Data Elements. | Prior to start date | Completed prior to start date |
| 2. Community consultation and notification for Exception from Informed Consent (EFIC) at study sites. | Prior to start date | Completed prior to start date |
| 3. Edit Manual of Procedures and Standard Operating Procedures for addition of ECoG. | Prior to start date | Completed prior to start date |
| 4. Approval of protocol and informed consent forms, with EFIC, at study site IRBs. | 3 | UT-H: prior to start<br>UP: prior to start<br>UC: month 5<br>UM: see below |
| 5. Approval of protocol and informed consent forms by Department of Defense Human Research Protections Office. | 1-3 | Expected: Nov 2017 |
| 6. Establish subaward contracts with Miami, UT-H, and Pittsburgh | 3 | UT-H: month 6<br>UP: month 11<br>UM: see below |
| 7. Installation of Moberg CNS monitors for ECoG recordings at study sites. | 1-2 | Completed by month 9 at UT-H, UP, and UC |
| 8. Site initiation visits and training. | 1-2 | UP: month 10<br>UT-H: pending<br>UM: see below |
| 9. Patient enrollment and data collection. | 4-36 | Not started |
| 10. Assessment of 6-month neurologic outcomes. | 10-42 | Not started |
| 11. Scoring of spreading depolarizations from patient recordings. | 5-39 | Not started |
| 12. Interim efficacy analysis after 60 patients accrued. | 22 | Not started |
| 13. Analysis of intracranial ECoG data in hypothermia vs. normothermia groups (Objective 2). | 40-45 | Not started |
| 14. Final analysis of neurologic outcomes of 120 patients (Objective 1). | 43-45 | Not started |
| 15. Manuscript preparation and publication. | 45-48 | Not started |

**Accomplishments toward these goals in Year 1**

**Overview**

The above table provides an overview of major study milestones and tasks with their projected times of completion compared with current status/progress. In the subsequent portions of this

section, we describe in more detail the specific progress accomplished for each task. The following bullet points summarize overall progress:

- We have completed all preparatory work concerning study design, procedures, materials, and resources required for study conduct
- The University of Miami has decided to withdraw from the study, and Emory University has been proposed as a substitute as the fourth study site.
- EFIC and study protocols have been approved by local IRBs at three study sites (UT-H, Pittsburgh, Cincinnati)
- Protocol and EFIC remain under review with Secretary of the Army's office; approval required prior to HRPO approval of protocols

**Study Procedures**
All study procedures were decided and finalized. This includes:

- protocol and manual for placement of ECoG strips
- protocol and manual for ECoG data collection using Moberg CNS
- determination of eCRF data fields and implementation in RedCap
- manual and procedures for upload/transfer of continuous recording data for central analysis, including deidentification

**Miami withdrawal; replacement by Emory**
In the third quarter; UC was informed that Miami decided to withdraw from the ECoG portion of this study. Thus, they will no longer be a performance site for this award. The decision was arrived at due to unspecified challenges with staffing and personnel at UM.

To compensate for this loss, the PI has discussed participation in the ECoG arm of the study with personnel at Emory University, a current HOPES study site. As per guidance from the USAMRAA Contract Officer, revised budgets and other required documentation is being prepared for approval of this suggested change to the SOW.

**Study IRB approval**
As a requirement for an EFIC study, the IRB approval from UT-H and associated documents were submitted for review by the Secretary of the Army in the first quarter. Throughout the year, the study team worked with Dr. Laura Brosch (Director, ORP, HRPO, USMRMC) to answer all queries and prepare additional documents as required for this review. No documents are outstanding, and the protocol remains under review at the end of Year 1, with a decision expected early in Year 2.

The below table summarizes protocol status for each study site. All sites have received local IRB approval and await Secretary of Army approval. Emory is listed as a potential replacement for Miami, pending USAMRAA approval.

| | **Cincinnati** | **UT-H** | **Pittsburgh** | **Emory** |
|---|---|---|---|---|
| **Local IRB** | Approved | Approved | Approved | Approved |
| **Secretary of the Army; ORP HRPO** | Under review | Under review | Under review | Addition of study site pending approval |
| **Site Initiation Visit** | N/A | | July 25, 2017 | |
| **Open for enrollment** | | | | |
| **Subjects enrolled** | | | | |

**Opportunities for training and professional development**
Nothing to Report

**Dissemination of results to communities of interest**
Nothing to Report

**Next reporting period**
In the next quarter, we will:

- Submit required documents for replacement of Miami by Emory as a performance site
- Following expected approval, establish subaward with Emory and acquire Moberg CNS for ECoG data collection
- Following expected Secretary of the Army approval of the UT-Houston protocol, submit required documentation for HRPO approval for each of the study sites
- Conduct site initiation and training visit to UT-Houston and Emory
- Open enrollment at all four sites

## 4. IMPACT

**Impact on the development of the principal discipline(s) of the project**
Nothing to report

**Impact on other disciplines**
Nothing to report

**Impact on technology transfer**
Nothing to report

**Impact on society beyond science and technology**
Nothing to report

## 5. CHANGES/PROBLEMS

**Changes in approach and reasons for change**
Nothing to report

**Actual or anticipated problems or delays and actions or plans to resolve them**

1) The required review by the Secretary of the Army for this EFIC study has taken over 10 months and considerably delayed the opening of study enrollment. We have been rapidly responsive to all information requests during the process in order to facilitate a timely review.
2) If the Secretary of the Army's review of EFIC is unfavorable, the overall study design will have to be reconsidered, since enrollments without EFIC could be unacceptably low. Options include extending the strict enrollment time window of 5 hours to, e.g., 12 or 24 hr, or broadening other enrollment criteria such as including all TBI patients requiring surgery and not just ASDH. These changes would decrease the chance of a favorable

HOPES trial outcome (i.e. improved outcome in patients undergoing hypothermia), but data from ECoG monitoring would still be highly informative.

3) The decision from Miami to withdraw from the study has slowed progress somewhat. However, we undertook discussions with Emory from early in the study concerning their possible future involvement. Their replacement of Miami should keep the study on track for enrollment. Since no subaward with Miami was executed, this change would not affect the overall budget.

**Changes that had a significant impact on expenditures**
Nothing to report

**Significant changes in use or care of human subjects**
Nothing to report

**Significant changes in use or care of vertebrate animals**
Not applicable

**Significant changes in use of biohazards and/or select agents**
Not applicable

## 6. PRODUCTS

**Publications, conference papers, and presentations**
Nothing to report

**Website(s) or other Internet site(s)**
Nothing to report

**Technologies or techniques**
Nothing to report

**Inventions, patent applications, and/or licenses**
Nothing to report

**Other Products**
Nothing to report

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

**What individuals have worked on the project?**
*Name:* Jed Hartings, PhD
*Project Role:* Principal Investigator
*Nearest person month worked:* 2
*Contribution to Project:* Established study procedures and protocols, coordinated with site PIs, organized work flow and priorities, conducted community consultations, coordinated with UT-Houston, supervised regulatory and research coordinators, coordinated acquisition of supplies and equipment.

*Name:* S. Iris Deeds, CCRP
*Project Role:* Clinical Research Coordinator
*Nearest person month worked:* 1
*Contribution to Project:* Ms. Deeds has served as lead research coordinator for the study at Cincinnati. She has organized and disseminated study documents, corresponded with UT-Houston personnel on study implementation/coordination, served as principal correspondent with each study site, supervised regulatory work and IRB correspondence, and performed site visits.

*Name:* Gigi Hergenroeder, MHA, RN
*Project Role:* Co-PI, HOPES
*Nearest person month worked:* 1
*Contribution to Project:* Dr. Hergenroeder has been principally responsible for coordinating and implementing DOD-requested changes to the study protocol at study sites and in preparing documentation for Secretary of the Army review. She coordinates with Dr. Hartings in preparing study procedures and implementing the study database.

**Changes in other support of the PD/PI(s) or senior/key personnel since the last reporting period**
Nothing to report

**Other organizations involved as partners**
Organization Name: University of Texas at Houston
Location of Organization: Houston, TX
Partner's contribution to the project: Overall management and integration of the study within the context of the HOPES trial. Study site enrolling subjects.
Financial support to project: None
In-kind support: None
Facilities, Collaboration, or Personnel Exchange outside contribution noted above: None

Organization Name: University of Pittsburgh
Location of Organization: Pittsburgh, PA
Partner's contribution to the project: Study site enrolling subjects.
Financial support to project: None
In-kind support: None
Facilities, Collaboration, or Personnel Exchange outside contribution noted above: None

## 8. SPECIAL REPORTING REQUIREMENTS

Quad Chart is submitted separately.

## 9. APPENDICES

None

# Hypothermia for Patients Requiring Evacuation of Subdural Hematoma: Effect on Spreading Depolarizations

Log No. 14241002

Award No. W81XWH-16-C-0161

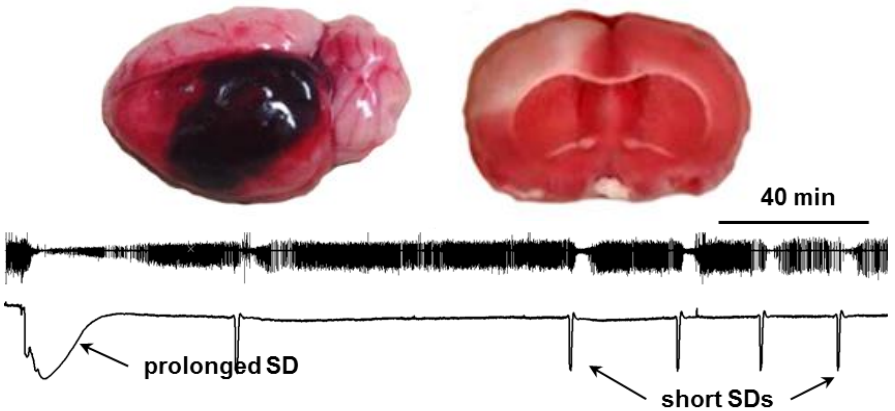
**PI:** Hartings, Jed A. **Org:** University of Cincinnati **Award Amount:** $1.035M

## Study/Product Aim(s)

1. In TBI patients requiring surgical evacuation of subdural hematoma, determine whether hypothermia decreases incidence of spreading depolarizations, as a hypothesized therapeutic target, compared to normothermic temperature management
2. Determine whether the burden of spreading depolarizations (during and after temperature management and in total) is associated with long-term neurologic outcome, and whether such association is independent of temperature management protocol

## Approach

As an addition to a separately funded trial of hypothermic vs. normothermic temperature management with intravascular catheters, subdural electrode strips will be used for electrocorticographic (ECoG) monitoring of spreading depolarizations during the period of temperature management and rewarming (n=120 total).




**Spreading depolarization mediate lesion development in rat model of acute subdural hematoma (ASDH).** Top left: Gross pathology of ASDH. Top right: cortical infarct (lacking red stain) after 4 hr. Bottom: intracortical recordings demonstrate repetitive SDs during the course of infarct maturation. Preventing SDs is the hypothesized mechanism of hypothermia's therapeutic benefit.

## Timeline and Cost

| Activities CY | 17 | 18 | 19 | 20 |
|---|---|---|---|---|
| Sites open for enrollment | | | | |
| Patient enrollment/monitoring | | | | |
| ECoG scoring | | | | |
| Results analysis / reporting | | | | |
| **Estimated Budget ($K)** | **$1785** | **$1150** | **$1138** | **$655** |

**Updated:** 24 Oct 17

## Goals/Milestones

**CY17 Goal** – Open enrollment

- ☑ Train and equip sites with supplies/monitoring equipment
- ❑ Ethical approvals at all sites and DOD/OHRP
- ❑ Open enrollment

**CY18-19 Goals** – Patient enrollment

- ❑ Patient enrollment and data collection
- ❑ Interim analysis with n=60 patients
- ❑ Scoring of ECoG data

**CY20 Goal** – Analyze results

- ❑ Analyze effects of temperature management on SD
- ❑ Analyze SD in relation to patient outcomes

**Comments/Challenges/Issues/Concerns:** 1) EFIC trial requires SecArm approval. 2) Enrollment expected to be slow

**Budget Expenditure to Date**

Y1 Projected Expenditure: $419K

Actual Expenditure: $77K